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Defining the ischemic penumbra using hyperacute neuro-imaging: Deriving quantitative ischemic thresholds

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Abstract

Despite three decades of promise, a neuro-imaging biomarker capable of delineating the ischemic penumbra is yet to be definitively demonstrated. Much progress has been made, especially with MR imaging. However, in order to rigorously define an imaging biomarker of the ischemic penumbra, carefully designed studies which can derive ischemic thresholds using quantitative imaging parameters may be required. Two thresholds are of interest: one which distinguishes the ischemic core from penumbra, and another which distinguishes the penumbra from benign oligemia. In this review, we discuss one possible approach to define these thresholds by following tissue fate in the presence or absence of early reperfusion.

The ischemic penumbra: from concept to clinical practice

The concept of the “ischemic penumbra,” first coined by Astrup in 1977, was based on almost a decade of research in a variety of gyrencephalic animal models of focal cerebral ischemia. These studies revealed two cerebral blood flow (CBF) thresholds of ischemia: an upper threshold which defined electrical failure in brain tissue, encompassing functionallyimpaired but structurally-intact neurons (which corresponded to a CBF of 15ml/100g/min); and a lower threshold below which intracellular potassium was released into the extracellular space, which was believed to represent functional and structural impairment (corresponding to 6ml/100g/min) [1–3]. Astrup posed that the penumbra represented tissue between these two thresholds, including “areas with less severe ischemia…with electrical failure but sustained energy metabolism and low extracellular potassium and with the possible potential for recovery”, in contrast to the ischemic core which he described as “areas of severe ischemia with energy failure, high extracellular potassium, and developing infarction” [4]. This technical definition of penumbra was later generalized and rewritten as “a zone of nonfunctioning but still viable tissue that may recover its function if blood flow can be restored, for example, by therapeutic intervention.” [5], and has been widely accepted

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today. Critical to this definition was the concept that ischemic brain tissue could be impaired but viable—as evidenced by subsequent survival of tissue after reperfusion. Also important was the concept that time was a critical component of viability. While reperfusion that occurred within a window of tissue viability could rescue brain tissue from death, reperfusion that occurred too late was ineffective for tissue survival.

Ultimate proof for the existence of the ischemic penumbra in human stroke came from clinical trials of reperfusion-promoting therapies demonstrating clinical benefit in patients treated with thrombolytic therapy (intravenous recombinant tissue plasminogen activator [tPA] and intra-arterial recombinant pro-urokinase)[6–8]. Thus, brain tissue that would have died without reperfusion was salvaged after thrombolysis, reflected by improved clinical outcome. Aggregate data from multiple thrombolytic trials also demonstrated a clear relationship between time interval from symptom onset to tPA treatment, and long-term clinical outcome [9]. In stroke populations, these studies suggest a relatively short time window for tissue salvage—intravenous and intra-arterial thrombolysis have demonstrated benefit only up to 4.5 hours and 6 hours after symptom onset, respectively [6–8], with diminishing efficacy for longer time intervals.

While the above definition of “ischemic penumbra” is based on tissue salvage in response to adequate and timely reperfusion, there is substantial evidence in animal models (but not humans) that brain tissue can be rescued from infarction using neuroprotective interventions independent of reperfusion[10]. These interventions aim to alter a variety of biochemical pathways involved in neural cells death cascades—each defining a different “penumbra”. Therefore, it has been suggested that a more appropriate term might be “preventable infarction” [11] in which tissue within regions of preventable infarction will die if untreated and will live if treated. Such a term encompasses tissue that may be salvaged by any therapy, not just reperfusion-promoting therapy. However, for the purposes of this article, we have focused on identification of tissue which will be salvaged by tissue reperfusion, thus utilizing the original term, “ischemic penumbra”.

Imaging the ischemic penumbra

Not long after the concept of the ischemic penumbra was conceived, several imaging methods were applied to acute ischemic stroke patients in attempt to delineate salvageable tissue. Early studies utilizing positron emission tomography (PET) revealed that CBF thresholds for brain function and tissue death were similar to those found in primates stroke models [12–14]. Moreover, a unique pattern of hemodynamic and metabolic change emerged during early phases of ischemia: reduced CBF associated with increased oxygen extraction fraction (OEF, the fraction of oxygen extracted from arterial blood) with preserved oxygen consumption ($CMRO_2$). This state was termed “misery perfusion” and was postulated to be a PET imaging signature of the ischemic penumbra [15]. The hallmark of this state was an increase in OEF in regions of low blood flow, resulting in a preservation of $CMRO_2$. Follow-up PET imaging demonstrated a dramatic decrease in OEF in some of these regions (with concomitant decline in $CMRO_2$), suggesting tissue progression to infarction [16], confirmed by longer-term imaging with CT. Brain tissue with $CMRO_2$ below a certain threshold value was thought to represent the lower limit of the penumbra. Performing

transient MCA occlusion in anesthetized baboons, Touzani et al. [17] concluded that $CMRO_2$ < 40% of the contralateral hemisphere predicted tissue with eventual infarction. Powers et al. [14] measured regional CBF and $CMRO_2$ in 50 patients with varying degrees of cerebral ischemia and established a minimum $CMRO_2$ of 1.3 ml/100g/min for maintaining brain viability, corresponding to 37–39% of normal values [18]. Importantly, unlike the CBF thresholds determined in earlier animal studies, $CMRO_2$ thresholds were thought to be independent of the time interval after stroke onset making it an ideal marker for identification of viable tissue in ischemic stroke patients[19]. However, such PET-derived markers are largely based on controlled primate MCA occlusion-reperfusion experiments; reperfusion studies in humans have not been performed, thus prohibiting any definitive statements about PET's ability to delineate the penumbra in humans.

More recent PET studies have evaluated potential biomarkers for delineating the ischemic core. In particular, ^{11}C-flumazenil (FMZ) binding to cerebral GABA receptors does not require arterial blood sampling as does calculation of $CMRO_2$, which are known to be sensitive to ischemia and neuronal loss, has been examined following transient MCA occlusion experiments in cats [20]. Increased FMZ-binding correlated well with $CMRO_2$ values for irreversible injury as well as the final infarction. In ischemic stroke patients, FMZ-binding also demonstrated moderate sensitivity and good specificity for infarcted tissue [21, 22]. Similar to other PET markers, these studies have not assessed how FMZ-binding may predict tissue infarction in reperfused compared to non-reperfused tissue in humans within a clinically-relevant time window, thus its potential as a penumbral marker is currently unclear.

In many ways, the ideal quantitative physiological imaging measures provided by PET have been clinically limited by logistical hurdles of utilizing this technology in hyper-acute ischemic stroke patients. Around the clock availability of short-lived isotopes, limited availability in specialized centers, and requirement for arterial lines, have limited PET studies in the hyperacute setting of stroke. Thus, alternative MR and CT imaging approaches have been extensively explored. Multi-modal MRI has shown tremendous promise. Diffusion weighted imaging (DWI) has been used to delineate irreversibly-injured tissue (i.e. the ischemic core) and perfusion weighted imaging (PWI) for delineating the extent of critically hypoperfused tissue that will evolve into infarction if not reperfused in a timely manner. When DWI and PWI are combined together, the non-overlapping region depicted by DWI and PWI (mismatch) is postulated to represent the penumbra [23–25]. Consistent with the idea of an evolving ischemic core, Baird et al. [26] and others demonstrated growth of the DWI lesion into a final infarct approximating the early PWI abnormality. However, studies have demonstrated that DWI lesions can reverse after reperfusion with subsequent tissue survival, suggesting that DWI lesions may not accurately represent the ischemic core [27, 28]; moreover, studies have suggested that the territory delineated by PWI abnormalities may overestimate the penumbra[29]. Regardless, the methodology has been rapidly translated into several human studies, demonstrating the potential clinical utility of DWI-PWI mismatch for selection of patients beyond the therapeutic window [23–25].

Like MR, CT perfusion has become more widely available. Wintermark et al. [30] identified a relative CBF of <34% of the contralateral hemisphere for delineating tissue that died in the

absence of reperfusion, but survived if reperfused. In one prospective multi-center study, acute ischemic stroke patients were imaged < 12 hours from stroke onset with CT and MRI [31]. The perfusion CT parameter most accurately reflecting the ischemic core (as compared to DWI) was absolute cerebral blood volume (CBV) < 2 ml/100g, while the parameter most accurately reflecting the penumbra was a relative mean transit time > 145% of the contralateral hemisphere. However, in more recent studies, relative CBF was found to be more predictive of the ischemic core and final infarct volume than absolute CBV [32–34]. In contrast to MR with its measurement of DWI, CT does not have as specific a marker of the ischemic core and therefore has not been translated into clinical studies as readily as MR.

While structural- and blood flow-based imaging markers of the penumbra have been a large focus of recent studies aimed at identifying salvageable tissue, an ideal marker of tissue viability would measure to what degree the metabolic demands of the tissue are being met. The putative time-invariance of the $CMRO_2$ threshold make it a potentially attractive index to define injury thresholds, unlike that of CBF which is time-dependent. To date, however, confirmation of tissue viability in regions of elevated OEF or confirmation of definite tissue infarction in regions of low $CMRO_2$ in hyper-acute ischemic stroke populations have not been possible due to the aforementioned practical limitations when attempting to image hyper-acute stroke patients with PET. Therefore, several investigations are ongoing in attempt to measure oxygen metabolism using MRI (MR-OMI, magnetic resonance-oxygen metabolic index) by taking advantage of the endogenous susceptibility of deoxyhemoglobin on T2* weighted images, in addition to several other novel methods [35–37].

Several imaging modalities and quantitative imaging parameters have been explored as potential biomarkers for defining the ischemic penumbra. Some of these parameters quantify physiological parameters (perfusion-related parameters, metabolism, etc), while others are empirically-derived (DWI). To take full advantage of the quantitative nature of the imaging parameters and how they may best predict eventual tissue fate, ideally, systematic methods will be used to define ischemic thresholds (for defining the upper and lower limit of the penumbra) prior to testing in clinical trials.

Defining the penumbra using reperfusion analysis

A major challenge for defining the penumbra using non-invasive imaging is the uncertainty of tissue fate in this brain region during hyperacute ischemia. To define the penumbra (tissue that will be salvaged from reperfusion), brain tissue that is already destined to die (core) must be distinguished from tissue that may survive if reperfused (penumbra), which must also be distinguished from tissue that is not at risk of dying (benign oligemia). Two thresholds are relevant in defining the penumbra: one which distinguishes core from penumbra, and a second which distinguishes penumbra from oligemia.

One hurdle in defining the ischemic core is that there is no imaging biomarker for brain tissue death (that is apparent immediately)—brain tissue that is fated to die usually takes many hours to reveal characteristic features of death (T2 or FLAIR signal). As discussed above, MR DWI appears within 30 min of ischemia and approximates the core, but evidence suggests that diffusion lesions are reversible with reperfusion, and when this occurs, heralds

better tissue survival rates than persistent diffusion lesions [27]. Thus, DWI may not be a reliable biomarker of the ischemic core. Therefore, another approach is needed whereby eventual tissue infarction can be correlated with early imaging characteristics that predict eventual tissue fate. This can be accomplished by co-registering hyperacute images with later time-point images (for example at 1 or 3 months) to determine which tissue eventually dies or survives, on a voxel-by-voxel basis.

In his original definition of penumbra, Astrup refers to "a zone of nonfunctioning but still viable tissue that may recover its function if blood flow can be restored." Therefore, reperfusion is a critical component for defining the penumbra, which is encompassed by the two thresholds described above. However, defining reperfusion at the tissue level requires imaging at two timepoints: one at baseline, and a second at a later time-point to define which tissue reperfused. Critically important is the choice of time-point for the 2nd image, as reperfusion may alter tissue outcome only if it occurs within a time-window of tissue viability. Thus, "effective reperfusion" must occur within this time window, in contrast to "ineffective reperfusion" in which perfusion is restored when tissue was already fated to die (Table 1)[11]. Based on clinical trials, outcomes are improved only if thrombolytics are administered within a 6-hour window [6–8]. Moreover, an analysis of IMS (Intervention Management of Stroke) patients demonstrated a time-dependent relationship between recanalization time and probability of good clinical outcome; the probability of good clinical outcome was greater than non-reperfused patients only if recanalization occured within 6 hours of symptom onset[38]. Therefore, one might make the assumption that, on average, 6 hours may represent the outside window for tissue viability (though it will likely vary from individual to individual).

Thus, in order to define brain tissue that falls within the ischemic penumbra, one must account for the reperfusion status of the brain tissue, and follow that tissue through time to determine its ultimate fate (death or survival). One approach that has been used to derive imaging thresholds that define the penumbra utilizes serial imaging to: 1) measure the imaging parameter of interest at baseline, 2) determine which tissue has reperfused within the viability window, and 3) determine which tissue eventually survives or dies. This imaging paradigm requires that acute ischemic stroke patients be imaged at three time-points (see Fig 1A). The earliest time-point (baseline) will acquire the quantitative imaging biomarker of interest. In addition, perfusion maps are acquired at this time-point. The second time-point, which will be acquired at the end of the presumptive tissue viability window (~6hrs), will identify regions of reperfusion (when compared to baseline perfusion maps). For this analysis, tissue-based reperfusion data (rather than recanalization) is required, as the reperfusion status of each voxel is needed for the final analysis. Finally, the third image will be acquired at 1–3 months after stroke to identify the region of final infarct (using FLAIR or T2 images), distinguishing tissue that survived from tissue that died. Co-registration of images obtained at these three time-points will permit voxel-by-voxel analysis—each voxel carried forward through time will have an initial baseline quantitative value (imaging biomarker of interest), carry a history of reperfusion/nonreperfusion (within the first 6 hours), and a determination of eventual tissue fate (viable or infarcted). Because this analysis depends on reperfusion status (regardless of treatment with thrombolytics), data from both treated and untreated patients can be used.

To determine the threshold for irreversible injury (tissue that dies regardless of reperfusion), brain regions that have reperfused are analyzed (Fig 1B, lower panel). Within this reperfused region, voxels that die will be segregated from voxels that survive, and the corresponding baseline value for the imaging biomarker of interest can be plotted in a frequency histogram (as shown in Fig 1C, lower panel). The threshold for irreversible injury will be the baseline value that best separates reperfused voxels that die from reperfused voxels that survive (Fig 1C, lower panel, purple dashed line). This threshold value can be determined using a variety of statistical methods (e.g., the optimization of Youden's index which maximizes sensitivity and specificity for prediction of tissue fate[39]). To determine the threshold for reversible injury, analysis is restricted to brain regions that have not reperfused (Fig 1B, upper panel). Voxels in these non-reperfused regions will be separated into tissue that survives (representing oligemic tissue) and tissue that dies (representing penumbral + core tissue). Thus, the baseline value that best separates voxels that die from those that survive represents the threshold for reversible injury (Fig 1C, upper panel, blue dashed line). Voxels (or brain tissue) with baseline values that fall between these two thresholds (for irreversible and reversible injury) represent the ischemic penumbra (Fig 1D).

As long as all three time-points are obtained, such an imaging analysis can be applied to virtually any quantitative imaging parameter (e.g. DWI-PWI mismatch, MR-OMI, etc.), to derive thresholds for reversible and irreversible injury based on reperfusion. Since the thresholds are derived on an individual-patient basis, a population-based average of each threshold must be obtained. The predictive performance of the population-derived thresholds (how well they predict tissue fate) can be subsequently tested in an independent population of patients (a different group of patients from which the thresholds were derived). Alternatively, the same patient population (from which the thresholds were derived) could serve as the "test" population, by using statistical re-sampling methods such as jackknifing, boot-strapping, or cross validation. The two thresholds will divide brain tissue into core, penumbra and oligemia, and their predictive value will be determined based on their ability to predict infarction or survival in reperfused and non-reperfused tissue as indicated in Table 1. Thus, tissue determined to be in the core should have a high probability of infarction regardless of reperfusion; tissue in the penumbra will have high probability of infarction in the absence of reperfusion, but high probability of salvage with reperfusion; and finally, tissue categorized as oligemic will have a high probability of survival regardless of reperfusion[5].

Several other computational methods to predict tissue outcome have been explored. Many of these methods have taken advantage of the multiparametric MR data collected during hyperacute stroke to create models that are highly predictive of tissue outcome. These approaches include voxel-by-voxel automated cluster analysis[40], iterative self-organizing data analsyis (ISODATA) [41], and generalized linear modeling (GLM) [42]. These predictive methods do not attempt to delineate the ischemic penumbra which requires knowledge of early reperfusion. Therefore, these approaches may have limited value in helping to guide acute management decisions. Indeed, the GLM approach has been shown to have lower predictive value in patients treated with thrombolysis compared to untreated patients[43], reflecting the predictive nature of the models only in the absence of reperfusion.

Regardless of method, once thresholds with high predictive value have been derived, the ultimate test of the imaging biomarker-derived threshold will be in therapeutic trials which utilize the imaging biomarker for patient selection.

Clinical studies testing penumbral imaging markers

Several clinical studies have been completed or are underway that have examined hyperacute neuro-imaging as a selection tool for therapy. These trials, which have specifically examined MR diffusion/perfusion mismatch (DPM), fall under three categories of study design: (1) one which utilizes DPM to select patients for enrollment in the therapeutic trial; these include studies such as Desmoteplase in Acute Ischemic Stroke trial (DIAS) [44], Dose Escalation for Ischemic Stroke trial (DEDAS) [45], and DIAS-II[46]; (2) one which aims to validate DPM as a biomarker of the penumbra, including studies such as Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution trial (DEFUSE) [47] and DEFUSE-2 [48, 49]; and (3) one which aims to do both such as Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET) [50] and Mechanical Recanalization of Stroke Clots Using Embolectomy study (MRRESCUE[51]).

These trials have demonstrated feasibility of testing an imaging biomarker as well as performing dual time-point imaging for measurement of reperfusion. The trials have also brought to light the importance of rigorous definition of ischemic thresholds. For example, DEFUSE was designed to validate DPM by comparing clinical outcomes in patients with DPM and reperfusion to patients without DPM and reperfusion; patients in both groups were treated with tPA between 3–6 hours of stroke onset [47]. All patients were serially imaged with MRI prior to tPA treatment (to assess for the presence of mismatch), and at 3–6 hours after tPA treatment (to assess for tissue reperfusion). DWI lesions were defined as > 3 standard deviations of the contralateral hemisphere and PWI lesions were defined as Tmax delay ≥ 2 sec. DPM was defined as PWI/DWI volume ≥ 1.2 and PWI-DWI volume ≥ 10 cc. Of 74 patients enrolled, after excluding patients with unsuccessful PWI scans or patients with a “small lesion profile”, 75% had DPM and 25% did not. In patients with DPM, reperfusion was associated with a significantly better clinical outcome than no reperfusion. However, due to the small number of patients without DPM (11 total), the converse (that non-mismatch patients did not improve with reperfusion) could not be proven, making it difficult to validate this penumbral imaging biomarker. The high ratio of mismatch to non-mismatch patients made it clear that the definition for DPM was too liberal, resulting in a relatively unselected group of stroke patients, a subset of whom unlikely had salvageable tissue. Using similar DPM thresholds, the EPITHET trial also found that only 14% of patients had non-mismatch profiles [50].

Based on these results, the DEFUSE investigators refined the DPM definition, and this new profile was used in the DEFUSE-2 study. DWI lesions were defined as ADC < 600 mm^2/sec and PWI lesions were defined as Tmax delay > 6 sec. DPM was defined as PWI/DWI≥1.8. However, beyond DPM, they selected a “target mismatch” group which excluded patients with very large baseline DWI (>70cc) and PWI (Tmax>10sec, >100cc) lesions since DEFUSE-1 indicated that these patients may have worse outcomes. The results of this study are forthcoming, but preliminary results look promising. Selection of patients with the

"target mismatch" definition demonstrated improved clinical outcome and reduced infarct growth compared to the non-target mismatch group [48, 49]. The DEFUSE experience underscores the importance of rigorously defining the imaging biomarker for penumbra, and illustrates an opportunity to explore more quantitative approaches in doing so.

Conclusion

There is great promise that neuro-imaging may provide signatures that delineate the ischemic penumbra. However, to define this elusive and transient state during hyperacute cerebral ischemia will require rigorous study design. Critical to the definition of penumbra is the required knowledge of the reperfusion status of tissue, requiring multiple time-point imaging. Two thresholds are relevant to defining the penumbra: the first is a threshold that distinguishes core from penumbra, and the second distinguishes penumbra from benign oligemia. After validation of ischemic thresholds in an independent patient population, the imaging thresholds can then be tested in clinical trials which utilize the biomarkers for patient selection. Such rigorous testing will help to ensure that the imaging biomarker (whether DPM or another imaging parameter) truly has potential to identify salvageable tissue with reperfusion-promoting therapies.

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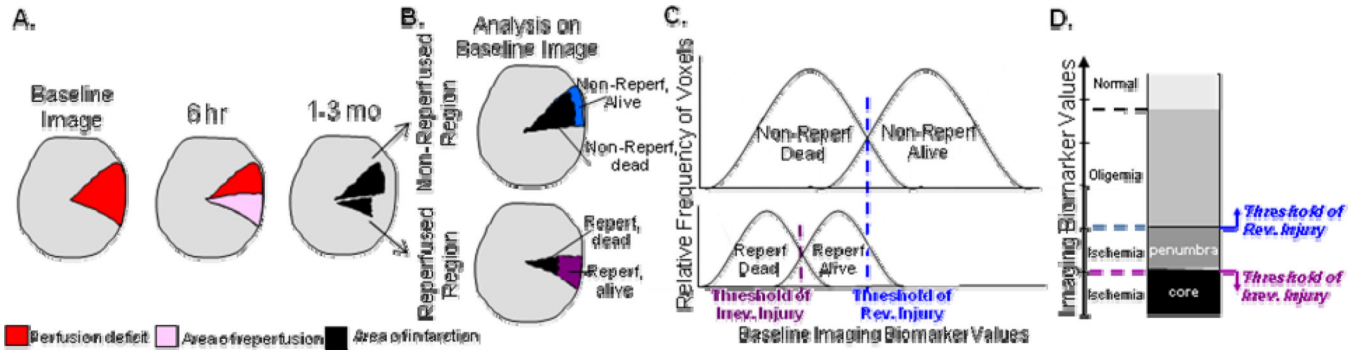

Figure 1. Defining Thresholds for a Penumbral Imaging Biomarker Based on Reperfusion

Baseline, 6 hr, and 1–3 month images are required to delineate baseline imaging values, reperfusion status, and final infarct. (B) Image co-registraton maps tissue reperfusion status and tissue fate (survival or death) on the baseline image and permits separate analysis of reperfused (lower panel) and non-reperfused (upper panel) tissue. (C) Frequency histograms of values of the baseline imaging biomarker are created from images in B. The baseline value which best separates surviving from dead tissue in non-reperfused regions (upper panel) marks the threshold of reversible injury (blue dashed line); while the baseline value which best separates surviving from dead tissue in reperfused regions (lower panel) marks the threshold of irreversible injury (purple dashed line). D. The penumbra falls between these two ischemic thresholds.

Table 1

§ Reperfusion-based model for separating ischemic core, penumbral, and oligemic brain tissue

	Irreversibly-Injured Tissue (core)	***Reversibly-Injured or Viable Tissue (penumbra)***	**Tissue with Benign Oligemia**
Non-reperfused	Tissue Dies	*Tissue Dies*	Tissue Survives
Reperfused	Tissue Dies **	*Tissue Survives**	Tissue Survives

§ Adapted from [11]

* Tissue with “Effective Reperfusion”

** Tissue with “Ineffective Reperfusion”